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Process for the Oxidation of Secondary Amines into the Corresponding Nitroxides

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Process for the Oxidation of Secondary Amines into the Corresponding Nitroxides

Nitroxides, in particular nitroxides of 2,2,6,6-tetraalkyl piperidine, are a very important class of compounds for various industrial applications. They are, for example, used as inhibitors to prevent premature polymerization of vinyl aromatic monomers during purification and distillation. They are also known as efficient stabilizers for organic materials, such as for thermosetting or thermoplastic polymers. Further applications for nitroxides are oxidation catalysts, polymerization regulators in controlled radical polymerization processes and spin labeling agents.

Numerous methods exist for their preparation. Some are for example described in L.B. Volodarsky, V. A. Reznikov, V.I. Ovcharenko.: "Synthetic Chemistry of Stable Nitroxides", CRC Press, Boca Raton, 1994. Oxidation of suitable secondary amines is among the most versatile ones.

Different oxidants can be used. From an industrial point of view, hydrogen peroxide, optionally together with various catalysts, t-butylhydroperoxide or peracids, in particular peracetic acid, are useful oxidants.

Peracids bring about a fast and often quantitative oxidation of the amine. It is particularly suitable for the oxidation of amines, which are difficult or impossible to oxidize with hydrogen peroxide, for example of highly sterically hindered amines.

One important parameter for the successful oxidation with a peracid is the pH of the reaction mixture. Thus, if the pH is too low, the oxidation may become too slow because the amine is exhaustively protonated. On the other side, if the pH is raised too much by the addition of a strong base such as e.g. sodium hydroxide, the peracid may decompose into oxygen and acid. This leads to the failure of the oxidation and poses additionally a serious security risk as the oxygen may form an explosive mixture with possibly present volatile organic compounds.

In WO 00/40550 it is suggested to solve this problem by adding simultaneously together with the peracid to the reaction mixture an aqueous solution of for example an alkali metal carbonate or bicarbonate. Peracid and base are simultaneously added as aqueous solutions to the stirred emulsion of water and amine, which is pre-dissolved in an appropriate organic solvent. The dosing rates of peracid and base are regulated in such a way that the pH is maintained in the range of 4 to 12.

Although this is a feasible method, such mode of operation gives rise to serious drawbacks:

- a) The apparatus must be equipped with two dosing units.
- b) Measuring of the pH is required. However, a reliable pH-measurement in heterogeneous mixtures is rather difficult, in particular in large scale production,
- c) Alkali metal bicarbonates have a rather low solubility in water. As a consequence, large volumes of solutions are required. Therefore, the volume yield is low, which negatively influences the economics of the operation.

These drawbacks make the prior art process less attractive for large-scale industrial oxidation processes.

The instant invention avoids these drawbacks and allows thus a substantially more efficient process, particularly when large-scale production is envisaged.

The invention relates to a process for the preparation of secondary nitroxide radicals from their corresponding secondary amines by oxidation with an organic peracid, comprising the steps

- a) adding to a reaction vessel a secondary amine, optionally together with an organic solvent and in one batch a base selected from the group consisting of alkali metal, alkaline earth metal or ammonium bicarbonates and alkaline earth metal or ammonium carbonates or mixtures thereof in the form of a solid together with water or as an aqueous slurry;
- b) dosing a peracid under stirring to the reaction mixture in an amount of 1,0 to 2,5 mol per mol of secondary amine; and
- c) isolating the organic phase.

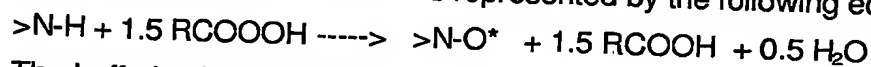
Preferably the organic solvent used in step a) is immiscible with water.

Examples are aromatic solvents, saturated hydrocarbon solvents or ketones.

The peracid may be any organic peracid, for example performic, peracetic, perpropionic, perbenzoic, m-chloroperbenzoic or trifluoroperacetic acid. Preferred is peracetic acid. The peracid may be used pure or in a suitable solvent. Preferred is the solution of peracetic acid in water or in acetic acid.

Preferably the amount of water added in step a) is sufficient to dissolve the organic acid salt formed in the neutralization reaction between the organic acid and the bicarbonate or carbonate.

The overall oxidation reaction is represented by the following equation:



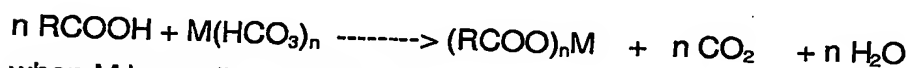
The buffering bases of the present invention are for example bicarbonates of alkali metals and alkaline earth metals (group 1+2 elements) or ammonium bicarbonate or carbonates of alkaline earth metals (group 2 elements) or ammonium carbonate. Mixed salts such as for example dolomite $\text{CaCO}_3 \cdot \text{MgCO}_3$ can also be used.

The bicarbonates or carbonates may also be partially replaced by alkaline earth hydroxides, for example calcium hydroxide or magnesium hydroxide.

Useful are for example also basic carbonates of alkaline earth metals of a general formula



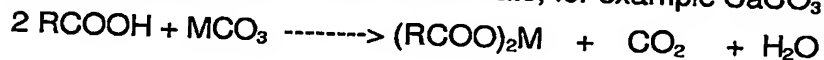
The buffering process consists of a partial or complete neutralization of the formed acid RCOOH according for example to:



when M is an alkali metal cation (Li^+ , Na^+ , K^+ , ...) or NH_4^+ , then $n=1$

when M is an alkaline earth metal cation (Ca^{++} , Mg^{++} , ...), then $n=2$

Or if an alkaline earth metal carbonate, for example CaCO_3 , is used:



The minimal volume of water in the process disclosed in WO 00/40550) for a given amount of bicarbonate is determined by its solubility in water at the given temperature. On the other hand, no or only little water is needed in the process of the present invention. Conveniently, a minimal amount of water may be added in the process of the present invention to ensure the formation of a homogeneous aqueous layer of the neutralized acids. Its amount is dictated by the solubility of the corresponding salts resulting from the organic peracid, for example acetates, if peracetic acid is used.

The carbonates of alkaline earth metals such as for example CaCO_3 , MgCO_3 or Dolomite ($\text{CaCO}_3 \cdot \text{MgCO}_3$) have such a low solubility in water that usefully concentrated solutions cannot be prepared. Thus, these carbonates would lead to an extremely low volume yield in the process disclosed in WO 00/40550.

A considerable further advantage of the above mentioned weakly basic bases is that their aqueous slurries do not trigger fast decomposition of the peracid. The difficult measurement of pH in a heterogeneous reaction system is therefore not necessary in the instant process. It is, however, mandatory in the prior art process.

To illustrate this, the solubility data of the technically most important bicarbonates and acetates are presented in Table 1.

Table 1

<u>Solubility</u>	Na ⁺	K ⁺	(NH ₄) ⁺	Ca ²⁺	Mg ²⁺
Bicarbonate	10.3 (25 °C) ^a	36.2 (25 °C) ^a	24.8 (25 °C) ^a	--	--
Acetate	50.4 (25 °C) ^a	269 (25 °C) ^a	148 (4 °C) ^a	43.7 (0 °C) ^b	65.6 (25 °C) ^a

(a) g/100g Water. (CRC Handbook of Chemistry and Physics, 82 nd Edition)

(b) g/100 g Solution. (R.K. Freier: "Aqueous Solutions", Walter de Gruyter, Berlin 1976)

Table 2 shows the minimal amount of water, calculated with the data from Table 1, which is needed for the preparation of a solution of 1 mol of bicarbonate to be dosed according to WO 00/40550.

The minimal amount of water needed to completely dissolve the acetate formed during the neutralization of 1 mol acetic acid with 1 mol of bicarbonate or 0.5 mol of carbonate loaded as a solid according to the present invention into the reactor is calculated for comparison. The water formed during the neutralization is not taken into consideration.

Table 2

	NaHCO ₃	KHCO ₃	NH ₄ HCO ₃	CaCO ₃	MgCO ₃
mL of H ₂ O WO 00/40550	815.5 (25 °C)	276.5 (25 °C)	318.5 (25 °C)	Unsoluble	Unsoluble
mL of H ₂ O Present Invention	162.7 (25 °C)	36.5 (25 °C)	52.0 (4 °C)	180.9 (0 °C)	108.5 (25 °C)

Table 2 clearly shows that the amount of the reactor volume occupied by the unproductive aqueous phase is substantially reduced in the process according to the present invention.

For example the base is sodium or potassium bicarbonate, calcium or magnesium carbonate or dolomite.

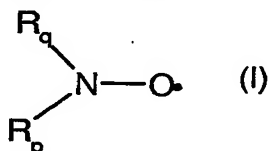
For instance the base is added in an amount of from 0.1 to 1.0 equivalent base per 1 equivalent of all acids present.

A suitable reaction temperature is between -20°C and 80°C , preferably between 0°C and 40°C .

Conveniently the dosage of the peracid is carried out from 10 minutes to 5 hours.

The total reaction time is for example from 30 minutes to 10 hours. The reaction is carried out, for instance, at atmospheric pressure.

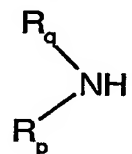
The nitroxide radical formed is for example of formula (I)



R_p and R_q are independently tertiary bound $\text{C}_4\text{-C}_{28}$ alkyl groups or $\text{C}_8\text{-C}_{17}$ secondary bound alkyl groups which are unsubstituted or substituted by one or more electron withdrawing groups or by phenyl; or

R_p and R_q together form a 5, 6 or 7 membered heterocyclic ring which is substituted at least by 4 $\text{C}_1\text{-C}_4$ alkyl groups and which may be interrupted by a further nitrogen or oxygen atom.

Consequently the secondary amine precursor is of formula (I')



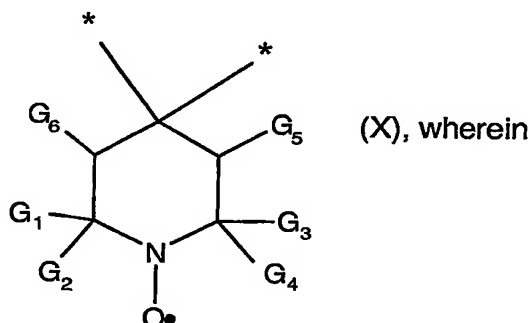
mostly items of commerce.

The nitroxyl radicals and their secondary amine precursors are principally known from US-A-4 581 429 or EP-A-621 878. Particularly useful are the open chain compounds described in WO 98/13392,

WO 99/03894 and WO 00/07981, the piperidine derivatives described in WO 99/67298 and GB 2335190 or the heterocyclic compounds described in GB 2342649 and WO 96/24620.

Further suitable nitroxylethers and nitroxyl radicals are described in WO 02/4805 and WO 02/100831

Examples of nitroxyl radicals, which can be prepared by the instant process are given below. For example the nitroxyl radical contains a structural element of formula (X)

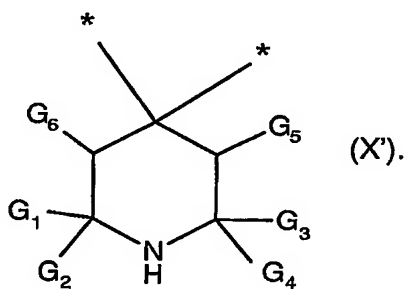


G_1, G_2, G_3, G_4 are independently C_1-C_6 alkyl or G_1 and G_2 or G_3 and G_4 , or G_1 and G_2 and G_3 and G_4 together form a C_5-C_{12} cycloalkyl group;

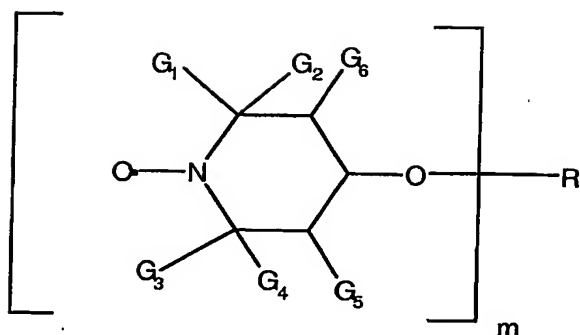
*denotes a valence; and

G_5, G_6 independently are H, C_1-C_6 alkyl.

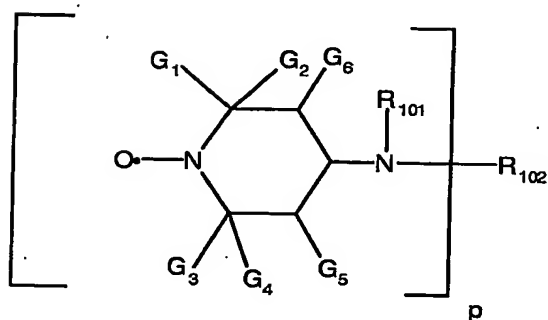
Consequently the amine precursor is of formula (X')



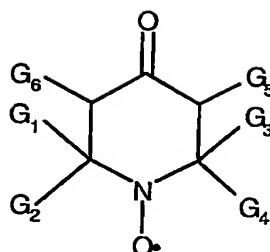
For instance the nitroxide radical is of formula A', B' or O',



(A')



(B')



(O')

wherein

m is 1,

R is hydrogen, C₁-C₁₈alkyl which is uninterrupted or interrupted by one or more oxygen atoms, cyanoethyl, benzoyl, glycidyl, a monovalent radical of an aliphatic carboxylic acid having 2 to 18 carbon atoms, of a cycloaliphatic carboxylic acid having 7 to 15 carbon atoms, or an α,β -unsaturated carboxylic acid having 3 to 5 carbon atoms or of an aromatic carboxylic acid having 7 to 15 carbon atoms;

p is 1;

R₁₀₁ is C₁-C₁₂alkyl, C₅-C₇cycloalkyl, C₇-C₈aralkyl, C₂-C₁₈alkanoyl, C₃-C₅alkenoyl or benzoyl;

R₁₀₂ is C₁-C₁₈alkyl, C₅-C₇cycloalkyl, C₂-C₈alkenyl unsubstituted or substituted by a cyano, carbonyl or carbamide group, or is glycidyl, a group of the formula -CH₂CH(OH)-Z or of the formula -CO-Z or -CONH-Z wherein Z is hydrogen, methyl or phenyl;

G₅ and G₆ are independently hydrogen or C₁-C₄alkyl, and

G₁ and G₃ are methyl and G₂ and G₄ are ethyl or propyl or G₁ and G₂ are methyl and G₃ and G₄ are ethyl or propyl.

More preferably in formula A', B' and O'

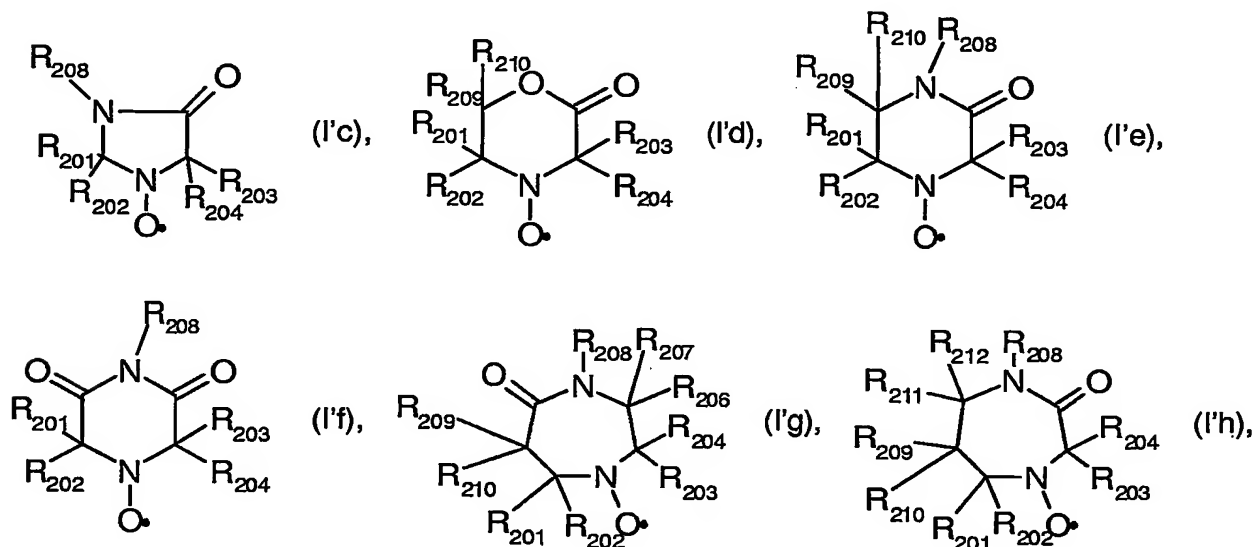
R is hydrogen, C₁-C₁₈alkyl, cyanoethyl, benzoyl, glycidyl, a monovalent radical of an aliphatic, carboxylic acid;

R₁₀₁ is C₁-C₁₂alkyl, C₇-C₈aralkyl, C₂-C₁₈alkanoyl, C₃-C₅alkenoyl or benzoyl;

R₁₀₂ is C₁-C₁₈alkyl, glycidyl, a group of the formula -CH₂CH(OH)-Z or of the formula -CO-Z, wherein Z is hydrogen, methyl or phenyl.

The above compounds, their precursors and their preparation are for example described in GB 2335190 and GB 2 361 235. Some are commercially available.

Another group of nitroxyl radicals are those of formula (Ic'), (Id'), (Ie'), (If'), (Ig') or (Ih')



wherein R₂₀₁, R₂₀₂, R₂₀₃ and R₂₀₄ independently of each other are C₁-C₁₈alkyl, C₆-C₁₈alkenyl, C₆-C₁₈alkinyl, C₁-C₁₈alkyl, C₃-C₁₈alkenyl, C₃-C₁₈alkinyl which are substituted by OH, halogen or a group -O-C(O)-R₂₀₅, C₂-C₁₈alkyl which is interrupted by at least one O atom and/or NR₂₀₅ group, C₃-C₁₂cycloalkyl or C₆-C₁₀aryl or R₂₀₁ and R₂₀₂ and/or R₂₀₃ and R₂₀₄ together with the linking carbon atom form a C₃-C₁₂cycloalkyl radical;

R₂₀₅, R₂₀₆ and R₂₀₇ independently are hydrogen, C₁-C₁₈alkyl or C₆-C₁₀aryl;

R₂₀₈ is hydrogen, OH, C₁-C₁₈alkyl, C₃-C₁₈alkenyl, C₃-C₁₈alkinyl, C₁-C₁₈alkyl, C₃-C₁₈alkenyl, C₃-C₁₈alkinyl which are substituted by one or more OH, halogen or a group -O-C(O)-R₂₀₅, C₂-C₁₈alkyl which is interrupted by at least one O atom and/or NR₂₀₅ group, C₃-C₁₂cycloalkyl or C₆-C₁₀aryl, C₇-C₉phenylalkyl, C₅-C₁₀heteroaryl, -C(O)-C₁-C₁₈alkyl, -O-C₁-C₁₈alkyl or -COOC₁-C₁₈alkyl; and

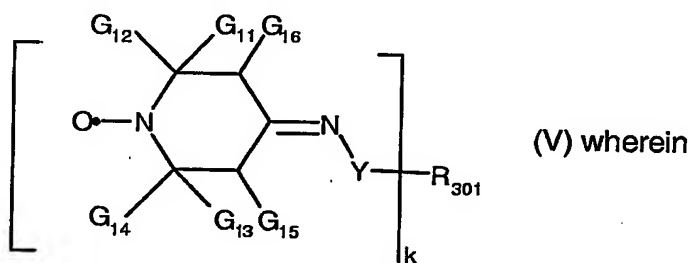
R₂₀₉, R₂₁₀, R₂₁₁ and R₂₁₂ are independently hydrogen, phenyl or C₁-C₁₈alkyl.

More preferably in formula (lc'), (ld'), (le'), (lf'), (lg') and (lh') at least two of R_{201} , R_{202} , R_{203} and R_{204} are ethyl, propyl or butyl and the remaining are methyl; or

R_{201} and R_{202} or R_{203} and R_{204} together with the linking carbon atom form a C_5 - C_6 cycloalkyl radical and one of the remaining substituents is ethyl, propyl or butyl.

The above compounds, their precursors and their preparation is described in GB 2342649.

Other suitable compounds are the 4-imino piperidine derivatives of formula V



G_{11} , G_{12} , G_{13} and G_{14} are independently C_1 - C_4 alkyl or G_{11} and G_{12} together and G_{13} and G_{14} together, or G_{11} and G_{12} together or G_{13} and G_{14} together are pentamethylene;

G_{15} and G_{16} are each independently of the other hydrogen or C_1 - C_4 alkyl;

k is 1, 2, 3, or 4

Y is O, NR_{302} or when n is 1 and R_{301} represents alkyl or aryl Y is additionally a direct bond;

R_{302} is H, C_1 - C_{18} alkyl or phenyl;

if k is 1

R_{301} is H, straight or branched C_1 - C_{18} alkyl, C_3 - C_{18} alkenyl or C_3 - C_{18} alkynyl, which may be unsubstituted or substituted, by one or more OH, C_1 - C_8 alkoxy, carboxy, C_1 - C_8 alkoxycarbonyl;

C_5 - C_{12} cycloalkyl or C_5 - C_{12} cycloalkenyl;

phenyl, C_7 - C_9 phenylalkyl or naphthyl which may be unsubstituted or substituted by one or more C_1 - C_8 alkyl, halogen, OH, C_1 - C_8 alkoxy, carboxy, C_1 - C_8 alkoxycarbonyl;

$-C(O)-C_1-C_{36}$ alkyl, or an acyl moiety of a $?, ?$ -unsaturated carboxylic acid having 3 to 5 carbon atoms or of an aromatic carboxylic acid having 7 to 15 carbon atoms;

$-SO_3^-Q^+$, $-PO(O^-Q^+)_2$, $-P(O)(OR_2)_2$, $-SO_2-R_2$, $-CO-NH-R_2$, $-CONH_2$, $COOR_2$, or $Si(Me)_3$, wherein Q^+ is H^+ , ammonium or an alkali metal cation;

if k is 2

R_{301} is C_1 - C_{18} alkylene, C_3 - C_{18} alkenylene or C_3 - C_{18} alkynylene, which may be unsubstituted or substituted, by one or more OH, C_1 - C_8 alkoxy, carboxy, C_1 - C_8 alkoxycarbonyl; or xylylene; or

R_{301} is a bisacyl radical of an aliphatic dicarboxylic acid having 2 to 36 carbon atoms, or a cycloaliphatic or aromatic dicarboxylic acid having 8-14 carbon atoms;

if k is 3,

R_{301} is a trivalent radical of an aliphatic, cycloaliphatic or aromatic tricarboxylic acid; and

if k is 4, R_{301} is a tetravalent radical of an aliphatic, cycloaliphatic or aromatic tetracarboxylic acid.

The compounds are described in WO 02/100831.

Preferably G_{16} is hydrogen and G_{15} is hydrogen or C_1 - C_4 alkyl, in particular methyl, and G_{11} and G_{13} are methyl and G_{12} and G_{14} are ethyl or propyl or G_{11} and G_{12} are methyl and G_{13} and G_{14} are ethyl or propyl.

The alkyl radicals in the various substituents may be linear or branched. Examples of alkyl containing 1 to 18 carbon atoms are methyl, ethyl, propyl, isopropyl, butyl, 2-butyl, isobutyl, t-butyl, pentyl, 2-pentyl, hexyl, heptyl, octyl, 2-ethylhexyl, toctyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, hexadecyl and octadecyl.

Alkenyl with 3 to 18 carbon atoms is a linear or branched radical as for example propenyl, 2-butenyl, 3-butenyl, isobutenyl, n-2,4-pentadienyl, 3-methyl-2-butenyl, n-2-octenyl, n-2-dodecenyl, isododecenyl, oleyl, n-2-octadecenyl oder n-4-octadecenyl.

Preferred is alkenyl with 3 bis 12, particularly preferred with 3 to 6 carbon atoms.

Alkynyl with 3 to 18 is a linear or branched radical as for example propinyl ($-\text{CH}_2-\text{C}\equiv\text{CH}$), 2-butenyl, 3butinyl, n2-octinyl, oder n2-octadecinyl. Preferred is alkynyl with 3 to 12, particularly preferred with 3 to 6 carbon atoms.

Examples for hydroxy substituted alkyl are hydroxy propyl, hydroxy butyl or hydroxy hexyl.

Examples for halogen substituted alkyl are dichloropropyl, monobromobutyl or trichlorohexyl.

C₂-C₁₈alkyl interrupted by at least one O atom is for example -CH₂-CH₂-O-CH₂-CH₃, -CH₂-CH₂-O-CH₃- or -CH₂-CH₂-O-CH₂-CH₂-CH₂-O-CH₂-CH₃-. It is preferably derived from polyethylene glycol. A general description is -((CH₂)_a-O)_b-H/CH₃, wherein a is a number from 1 to 6 and b is a number from 2 to 10.

C₂-C₁₈alkyl interrupted by at least one NR₅ group may be generally described as -((CH₂)_a-NR₅)_b-H/CH₃, wherein a, b and R₅ are as defined above.

C₃-C₁₂cycloalkyl is typically, cyclopropyl, cyclopentyl, methylcyclopentyl, dimethylcyclopentyl, cyclohexyl, methylcyclohexyl or trimethylcyclohexyl.

C₆-C₁₀ aryl is for example phenyl or naphthyl, but also comprised are C₁-C₄alkyl substituted phenyl, C₁-C₄alkoxy substituted phenyl, hydroxy, halogen or nitro substituted phenyl. Examples for alkyl substituted phenyl are ethylbenzene, toluene, xylene and its isomers, mesitylene or isopropylbenzene. Halogen substituted phenyl is for example dichlorobenzene or bromotoluene.

Alkoxy substituents are typically methoxy, ethoxy, propoxy or butoxy and their corresponding isomers.

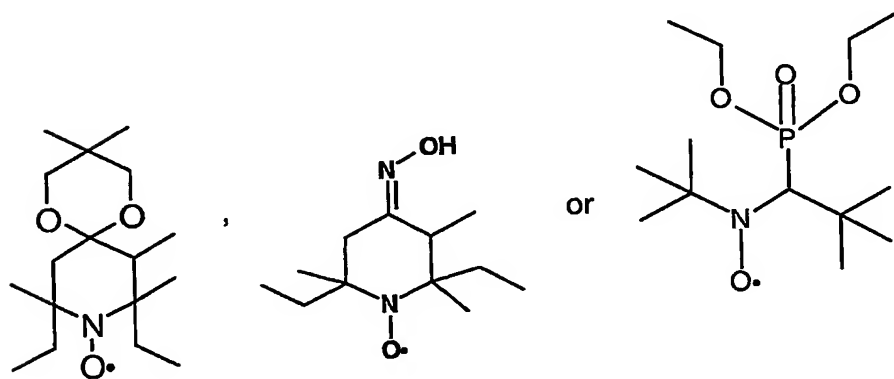
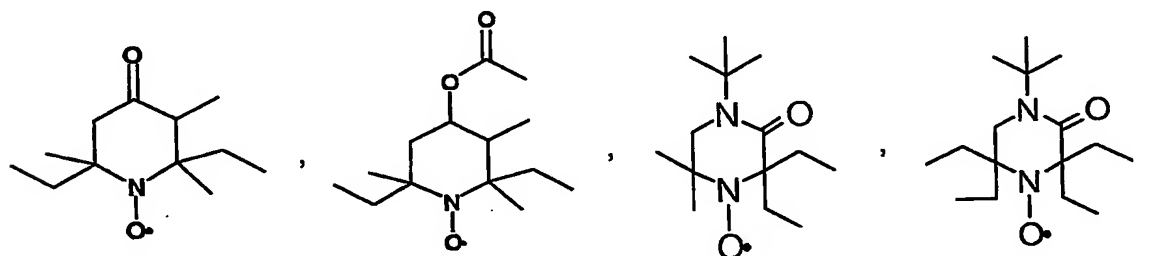
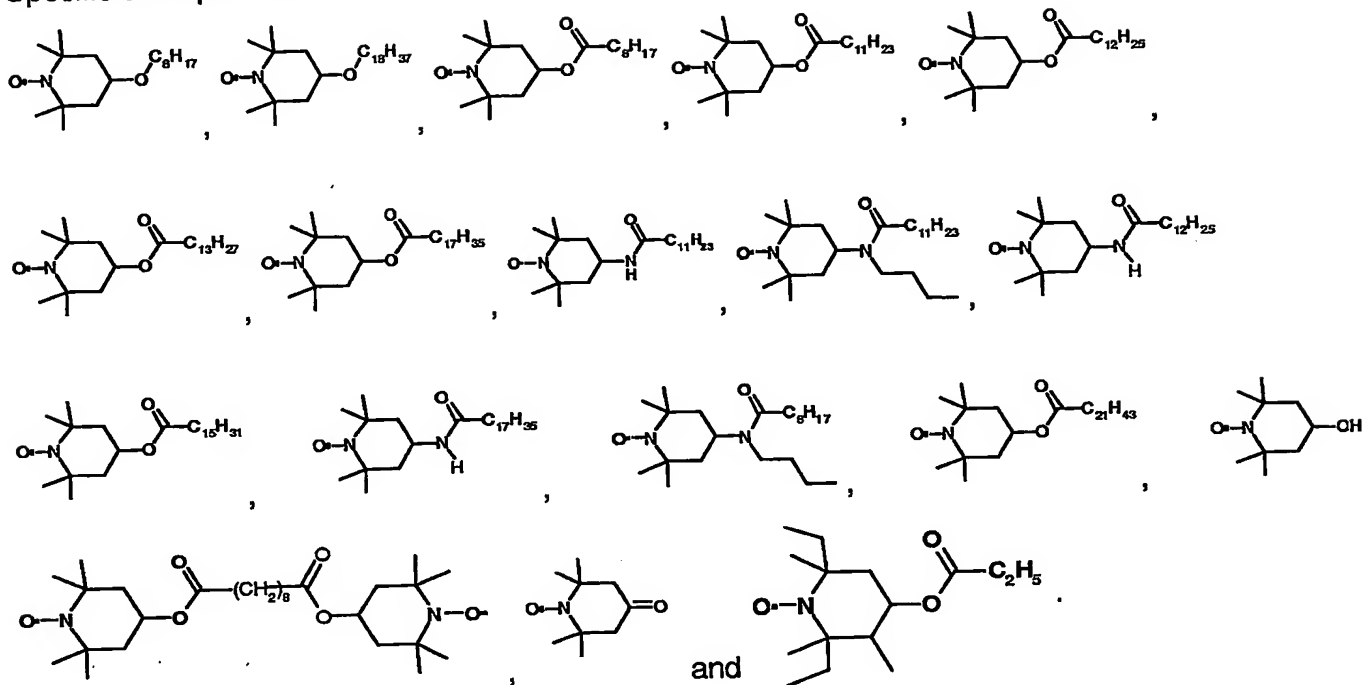
C₇-C₉phenylalkyl is benzyl, phenylethyl or phenylpropyl.

C₅-C₁₀heteroaryl is for example pyrrol, pyrazol, imidazol, 2, 4, dimethylpyrrol, 1-methylpyrrol, thiophene, furane, furfural, indol, cumarone, oxazol, thiazol, isoxazol, isothiazol, triazol, pyridine, α-picoline, pyridazine, pyrazine or pyrimidine.

If R is a monovalent radical of a carboxylic acid, it is, for example, an acetyl, propionyl, butyryl, valeroyl, caproyl, stearoyl, lauroyl, acryloyl, methacryloyl, benzoyl, cinnamoyl or β-(3,5-di-tert-butyl-4-hydroxyphenyl)propionyl radical.

C₁-C₁₈alkanoyl is for example, formyl, propionyl, butyryl, octanoyl, dodecanoyl but preferably acetyl and C₃-C₅alkenoyl is in particular acryloyl.

Specific examples are:



The compounds mentioned above are partially commercially available or they are prepared from the corresponding tetramethyl piperidines by known methods. Higher alkyl substituted piperidines and their preparation are for example described in GB 2 335 190 and in GB 2 361 235. The following examples illustrate the invention.

Example 1:

Oxidation of 2,6-Diethyl-2,3,6-trimethyl-piperidine-4-one using $\text{CH}_3\text{COOOH}/\text{CaCO}_3$

A four neck flask equipped with stirrer, thermometer and dropping funnel is charged with powdered calcium carbonate (20 g, 0.2 mol), water (75 ml), toluene (30 ml) and 2,6-diethyl-2,3,6-trimethyl-piperidine-4-one (19.73 g, 0.1 mol, prepared as described in Ger. Offen. DE 2623422). Peracetic acid (30.4 g, 0.16 mol, 40 % solution in acetic acid) is then added dropwise over 50 minutes to the stirred mixture while keeping the temperature between 20-30 °C. The mixture is then stirred for additional 150 minutes. The red organic layer is separated, washed with saturated NaHCO_3 and water, dried over MgSO_4 and evaporated to yield 19.26 g of 2,6-diethyl-2,3,6-trimethyl-piperidin-4-one-N-oxyl as a red liquid. The material is identical with the sample prepared as described in DE 19909767.

Example 2:

Oxidation of 2,6-Diethyl-2,3,6-trimethyl-piperidine-4-one using $\text{CH}_3\text{COOOH}/\text{MgCO}_3$

Magnesium carbonate (12.65 g, 0.15 mol) is employed in the same manner as described in example 1, using only 35 ml of water to yield 21.1g of 2,6-diethyl-2,3,6-trimethyl-piperidine-4-one-N-oxyl as a red liquid. The material is identical with the sample prepared as described in DE 19909767.

Example 3:

Oxidation of 2,6-Diethyl-2,3,6-trimethyl-piperidine-4-one using $\text{CH}_3\text{COOOH}/4\text{MgCO}_3 \cdot \text{Mg}(\text{OH})_2 \cdot 5\text{H}_2\text{O}$

The mixed magnesium carbonate-hydroxide of the formula $4\text{MgCO}_3 \cdot \text{Mg}(\text{OH})_2 \cdot 5\text{H}_2\text{O}$ (Fluka) (14.56g, 0.03 mol) was employed in the same way as described in example 2 to yield 20.25 g of 2,6-diethyl-2,3,6-trimethyl-piperidine-4-one-N-oxyl as a red liquid. The material is identical with the authentic sample prepared as described in DE 19909767.

Example 4:

Oxidation of 2,6-Diethyl-2,3,6-trimethyl-piperidin-4-one using $\text{CH}_3\text{COOOH}/\text{NH}_4\text{HCO}_3$

Ammonium bicarbonate (23.72g, 0.3 mol) is employed in the same way as described in example 1 using only 20 ml of water to yield 20.52 g of 2,6-diethyl-2,3,6-trimethyl-piperidine-4-one-N-oxyl as a red liquid. The material is identical with the authentic sample prepared as described in DE 19909767.

Example 5:

Oxidation of 2,6-Diethyl-2,3,6-trimethyl-piperidine-4-one using $\text{CH}_3\text{COOOH}/\text{KHCO}_3$

Potassium bicarbonate (30.03g, 0.3 mol) is employed in the same way as described in example 1 using only 11 ml of water and 30 ml of ethyl acetate instead of toluene to yield 20.77 g of 2,6-diethyl-2,3,6-trimethyl-piperidine-4-one-N-oxyl as a red liquid. The material is identical with the authentic sample prepared as described in DE 19909767.

Example 6:

Oxidation of 2,6-Diethyl-2,3,6-trimethyl-piperidine using $\text{CH}_3\text{COOOH}/\text{NaHCO}_3$

A four neck flask equipped with stirrer, thermometer and dropping funnel is charged with sodium bicarbonate (25.20 g, 0.3 mol), water (25 ml), ethylacetate (25 ml) and 2,6-diethyl-2,3,6-trimethyl-piperidine (9.17 g, 0.05 mol, prepared as described in WO 0046202). Peracetic acid (19.01 g, 0.1 mol, 40 % solution in acetic acid) is then added dropwise over 50 minutes to the stirred mixture while keeping the temperature between 20-30 ° C. The mixture is then stirred for additional 10 hours. The red organic layer is separated, washed with saturated NaHCO_3 and water, dried over Na_2SO_4 and evaporated to yield 9.63 g of 2,6-diethyl-2,3,6-trimethyl-piperidine-N-oxyl as a red liquid. The material is identical with the authentic sample prepared as described in DE 2621841.

Example 7:

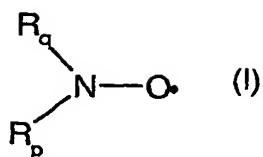
Oxidation of 2,2,6,6-Tetramethylpiperidin-4-one using $\text{CH}_3\text{COOOH}/\text{NaHCO}_3$

A four neck flask equipped with stirrer, thermometer and dropping funnel is charged with sodium bicarbonate (101.8 g, 1.2 mol), water (100 ml), ethylacetate (100 ml) and 2,2,6,6-tetramethylpiperidin-4-one (31.05 g, 0.2 mol, Aldrich). Peracetic acid (19.01 g, 0.1 mol, 40 % solution in acetic acid) is then added dropwise over 50 minutes to the stirred mixture while keeping the temperature between 20-30 ° C. The mixture is then stirred for additional 30 minutes. The reaction

mass is transferred into a separatory funnel, water (500 ml) is added and the red organic layer is separated. The aqueous layer is extracted with ethyl acetate (2 x 200 ml). The extracts and the organic layer are combined, dried over Na_2SO_4 and evaporated. The oily residue is crystallized from 50 ml hexane to yield 29.6 g of 2,2,6,6-tetramethylpiperidin-4-one-N-oxyl as a red solid. The material is identical with the authentic sample obtained from Aldrich.

Claims

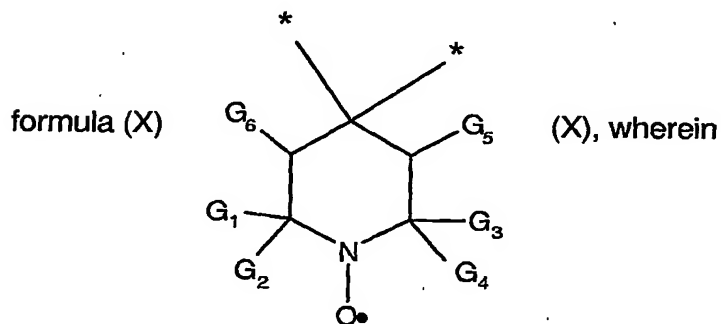
1. A process for the preparation of secondary nitroxide radicals from their corresponding secondary amines by oxidation with an organic peracid, comprising the steps
 - a) adding to a reaction vessel a secondary amine, optionally together with an organic solvent and in one batch a base selected from the group consisting of alkali metal, alkaline earth metal or ammonium bicarbonates and alkaline earth metal or ammonium carbonates or mixtures thereof in the form of a solid together with water or as an aqueous slurry;
 - b) dosing a peracid under stirring to the reaction mixture in an amount of 1,0 to 2,5 mol per mol of secondary amine; and
 - c) isolating the organic phase.
2. A process according to claim 1 wherein the organic solvent optionally used in step a) is immiscible with water.
3. A process according to claim 1 wherein the peracid is peracetic acid.
4. A process according to claim 1 wherein the amount of water added in step a) is sufficient to dissolve the organic acid salt formed in the neutralization reaction between the organic acid and the bicarbonate or carbonate.
5. A process according to claim 1 wherein the base is sodium or potassium bicarbonate, calcium or magnesium carbonate or dolomite.
6. A process according to claim 1 wherein the base is added in an amount of from 0.1 to 1.5 equivalents base per 1 equivalent of all acids present.
7. A process according to claim 1 wherein the reaction temperature is between 0° C and 40° C.
8. A process according to claim 1 wherein the dosage of the peracid is carried out from 10 minutes to 5 hours.
9. A process according to claim 1 wherein the nitroxide radical is of formula (I)



R_p and R_q are independently tertiary bound C_4 - C_{28} alkyl groups or C_8 - C_{17} secondary bound alkyl groups which are unsubstituted or substituted by one or more electron withdrawing groups or by phenyl; or

R_p and R_q together form a 5, 6 or 7 membered heterocyclic ring which is substituted at least by 4 C_1 - C_4 alkyl groups and which may be interrupted by a further nitrogen or oxygen atom.

10. A process according to claim 1 wherein the nitroxide radical contains a structural element of



G_1 , G_2 , G_3 , G_4 are independently C_1 - C_6 alkyl or G_1 and G_2 or G_3 and G_4 , or G_1 and G_2 and G_3 and G_4 together form a C_5 - C_{12} cycloalkyl group;

*denotes a valenc; and

G_5 , G_6 independently are H, C_1 - C_6 alkyl.

Abstract

The invention relates to a process for the preparation of secondary nitroxide radicals from their corresponding secondary amines by oxidation with an organic peracid, comprising the steps

- a) adding to a reaction vessel a secondary amine, optionally together with an an organic solvent which is immiscible with water and in one batch a base selected from the group consisting of alkali metal, alkaline earth metal or ammonium bicarbonates and alkaline earth metal or ammonium carbonates or mixtures thereof in the form of a solid together with water or as an aqueous slurry;
- b) dosing a peracid under stirring to the reaction mixture in an amount of 1,5 to 2,5 mol per mol of secondary amine; and
- c) isolating the organic phase.